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| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/007,385 | CHU, HSIEN- JUE | |
| | Examin r | Art Unit | |
| | Sharon L. Turner | 1647 | |

*-- The MAILING DATE of this communication app ars on th cover sh t with the correspond nce address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,5-8,11-14,16,18-21,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 5-8, 11-14, 16, 18-21 and 23-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## Response to After Final Amendment

1. The amendment and declaration filed 11-12-02 have been entered into the record and have been fully considered.

2. Upon review of the after final amendment and further consideration by the Examiner, the finality of the previous office action is hereby withdrawn. The finality has been withdrawn due to Applicants persuasive arguments with respect to previously withdrawn claims which are now included in the 103 rejection of record, largely for the same reasons of record.

3. Claim 22 is canceled. Claims 2, 5-8, 11-14, 16, 18-21 and 23-24 are pending.

4. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the Examiner.

## Election/Restriction

5. Withdrawal of newly submitted claims 24 and 18-21 has been reconsidered in view of Applicant's after final amendment. The claims are hereby regrouped into the claims under examination and will be addressed herein.

## Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 2, 5-8, 11-14, 16, 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as set forth in Paper No. 15, 18, 26 and as set forth herein, as being unpatentable over US Patent No. 5,183,659, Timoney et al, 2 February, 1993, in view of EP0786518 A1, Hartford et al, 24 January 1997, and US Patent No. 5,597,807, Estrada et al., 28 January 1997 as further evidenced by Timoney et al., Recent advances in streptococci and streptococcal diseases (1985) pp. 294-5, Proceed. Of the IXth Lancefield Int'l Symp. on Strep. and Strep. Diseases, Japan, September 1984, Reedbooks Ltd., Chertsey.

Timoney et al, teach a live non-encapsulated attenuated S. equi strain designated strain 70-297 (ATCC 53185) which is identical to applicants S. equi strain 70-297 deposited as ATCC Accession No. 53186. Applicants argue that this strain is publicly available since 1993, see Amendment A, Paper No. 5, mailed 3-26-99, paragraph spanning pp. 2-3. This strain is applicants preferred embodiment as recited in instant claims 5, 9, 11-14, 16, and 18. The page and line references cited herein are in respect to the '659 patent. Timoney teach that the vaccine may be administered either intranasally (mucosally) or orally see in particular abstract, that the vaccine is avirulent (attenuated) see in particular column 2, lines 57-64, and stimulates an immunological response which produces major IgG and IgA antibody in the nasopharyngeal mucus see in particular column 3, lines 40-45 and Figure 1. The strain is avirulent at 3X109 CFU when inoculated intranasally or orally. The strain is nonencapsulated, in particular column 4, lines 53-55. Vaccination either intranasally or

orally at 3X109 CFU produced resistance to challenge with wild-type virulent strain, see in particular Figure 2. In addition, the vaccine dosages are of amounts deemed to stimulate an antibody response in the nasopharyngeal mucosa of the susceptilble horse, see in particular claims 2-3. The vaccine is protective as claimed in claims 1-4 and 9-10 and is effective in abrogating the mortality (a symptom) associated with disease, see in particular columns 5-6.

Timoney et al do not teach the above vaccine in combination with an immunostimulant, the immunostimulant having the property of stimulating mucosal immunity.

Hartford, EP0786518 teach a protective live attenuated nasal mucosa S. equi vaccine for protective treatment/immunization against strangles in horses similar to Timoney, but in contrast to Timoney the Hartford vaccine is administered in combination with an immunostimulant which comprises Quil A (saponin) adjuvant to enhance the immune response of the host, see in particular p. 3, lines 39-46. Hartford does not expressly teach that Quil A saponin adjuvant has the property of stimulating mucosal immunity.

US Patent No. 5,597,807, Estrada et al teach Quinoa saponin compositions and methods of use. In particular, Estrada teaches Q. saponin compositions useful as immunological adjuvants, to stimulate nonspecific immunity, to enhance an immunological response to a selected antigen and to enhance mucosal absorption of a drug, see in particular abstract, column 1, lines 48-67. Estrada teaches the discovery that Q. Saponin composition can promote mucosal immunity, i.e., the production of IgG and IgA antibodies and enhances both humoral and secretory immune responses in vertebrates when administered with a selected antigen, see in particular column 5, lines 39-45. Estrada also teaches that Q. saponins enhance nonspecific immunity and cause

increased absorption through mucosal membranes, see in particular column 6, lines 57-67. Estrada teaches that Q. saponins can be used as immunological adjuvants in vaccine compositions and as absorption adjuvants, including against selected bacterial pathogens, see in particular column 6, lines 13-67. Estrada teaches in saline doses of Q. saponins at 2µg-10mg, see in particular Table 1 and with antigens of from .1-1000µg, see in particular column 8, lines 5-8.

Thus, Hartford teaches the benefit of combining a live attenuated nasal mucosa S. equi vaccine with an immunostimulant adjuvant, specifically Quil A , a saponin. Estrada teaches that Quinoa (Quil A) saponins provide the properties of enhancing mucosal immunity, increased mucosal antigenic absorption and stimulation of secretory IgG and IgA antibody.

Thus, it would have been prima facie obvious to one of skill in the art to modify the Timoney nasal (mucosal) vaccine by adding a Quil A saponin mucosal adjuvant to achieve the beneficial effects of enhanced mucosal immunity. One of skill in the art would be motivated to perform such modifications based on the teachings of the beneficial results of the adjuvant in S. equi vaccines, the effectiveness of Quil A saponins in vaccines producing enhanced mucosal immunity. One of skill in the art would have expected success using these methods based on the protective properties of the S. equi vaccines of Hartford and Timoney, and the beneficial results of an adjuvant as taught by Hartford and Estrada in producing enhanced mucosal immunological responses. In particular, one of skill in the art would have expected the effects of stimulating an immune response, providing protective immunity and preventing at least one of the symptoms associated with streptococcus equi infection via administration to the nasopharyngeal mucosa the claimed vaccine comprising administration of a live non-encapsulated attenuated streptococcus equi in combination

with a saponin immunostimulant. As extensively set forth the Timoney vaccine provides such properties upon administration to the nasal mucosa. The art expects that saponin would only enhance such effects. Thus, the composition, effects and method of administration to provide such effects would be obvious to the artisan at the time of the invention in view of the cumulative reference teachings. Thus, the reference teachings render the claimed invention obvious.

Applicants arguments filed 3-13-02 are essentially as previously set forth in the record. Applicants additionally argue hindsight reconstruction by the examiner and particularly argue that the combined references do not provide for the enhanced protective immunological effect demonstrated by the claimed saponin/attenuated S. equi vaccine. Applicants argue and submit a declaration by Dr. Li to provide evidence of non-obviousness as to a vaccine which induces an immune response and which is protective in horses. The relevancy of an antibody response and adverse side-effects are also discussed. Applicants argue and submit a declaration as to the inability to extrapolate the data in mice to effects in horses and to establish protective immunity based upon data such as antibody response. Applicants arguments and declaration outline three bases for rejection, which are not directly on point as expressed by the Examiner, see previous rejection of record.

Applicant's arguments and declaration filed 3-13-02 have been fully considered but they are not persuasive. Applicants arguments as to a "demonstration of an enhanced immunological effect" is not recognized by the Examiner as it is noted that no direct comparison of the Timoney vaccine with and without saponin or other adjuvants has been conducted. As previously noted, the vaccine of Timoney is already recognized for its protective properties, see in particular claims. Thus the protective effect of the vaccine does not appear to be in question. The question of relevancy is

whether or not the artisan would have found it obvious to combine the Timoney vaccine with saponin to arrive at the composition claimed as well as the method of stimulating an immune response with the modified composition claimed. In this respect, the literature is clear based on Hartford and Estrada that amongst other adjuvants, saponins are recognized to stimulate an immune response upon administration that is generally more beneficial than the selected antigen presented alone. Thus, the cumulative reference teachings would only be expected to improve the immune response and protection achieved via the Timoney vaccine with the combination of saponin. As to amended claims 22 and 23, it is noted that the composition is suitable for nasal administration as set forth in Timoney and that the vaccine is effective to provide protective immunity following challenge as noted in column 5-6 of Timoney the vaccinated horses which would be naturally exposed to S. equi challenge would have been expected to have strangles occurrence in 40% of the horses by at that date, only 2 horses exhibited disease. The comments of the previous action are appended for completion.

In paragraphs 1-2 of the traversal on 3-13-02 Applicants argue that Timoney is silent as to adjuvants and thus it is not obvious from Timoney to use saponin as an adjuvant. Applicants argue that absence a suggestion that the adjuvant saponin has immunostimulatory properties and that such an adjuvant would provide a protective immune response to challenge to disease one would not be motivated to modify Timoney to arrive at the invention.

In response, Hartford suggests that the adjuvant saponin has immunostimulatory properties such that it provides a protective immune response against disease challenge. In particular, Hartford teaches protection via a live attenuated nasal mucosa S. equi vaccine in combination with an immunostimulant that comprises Quil A

(saponin) adjuvant to enhance the immune response of the host to the invading pathogen, see in particular p. 3, lines 39-46.

In paragraph 3 of the traversal on 3-13-02 Applicants argue that Hartford and Estrada do not remedy the deficiencies of Timoney, in particular that Quil A (saponin) is but one adjuvant included in the deletion vaccine of Hartford but that such adjuvant is not exemplified. Applicant's argue that Hartford does not teach or suggest that any adjuvant stimulates mucosal immunity and does not teach or suggest that Quil A is an immunostimulatory adjuvant.

In response, Hartford does teach that Quil A is a known adjuvant that stimulates the immune system and enhances the immune response of the host, see in particular p. 3, lines 39-46. In addition, Estrada specifically teaches that saponins Quillaja and Quinoa stimulate IgG and IgA, mucosal specific immunity, see in particular Estrada, Figures 1-6, and columns 5-8.

In paragraph 4 of the traversal on 3-13-02 Applicants argue that Estrada also fails in that Quinoa saponin is but one specific type of saponin that surprisingly stimulates an immune response when administered mucosally, but that Estrada does not use S. equi or a comparable antigen and thus Estrada does not teach or suggest that an immune response may be achieved using the combination of Quinoa saponin and S. Equi or a comparable bacterial or disease causing antigen. Applicants further argue that neither does Estrada teach that Quinoa saponin provides protection from infection in the face of challenge.

In response, Estrada is not solely relied upon for such teachings. It is Hartford and Estrada which in particular cumulatively teach that Quillaja (Quil A) and Quinoa saponins are effective in stimulating immunity including mucosal immunity as evidenced by production of IgG and IgA as exemplified in Estrada and in promoting S. equi specific

immune responses as is taught by Estrada, column 5, line 36-column 6, line 52 and Hartford p. 3, lines 39-46, Examples 1-IV, Results and also the Conclusion.

In paragraphs 5-8 of the traversal on 3-13-02 Applicants argue that Estrada's teachings are unexpectedly different than Quil A saponin and thus that there is no reasonable expectation that such adjuvants would provide an enhanced immune response or protection in horses. Applicants acknowledge that Estrada teaches Quinoa saponin increased IgG and IgA, however they subsequently argue that such an immunological response is not predictive of protective immunity in the face of challenge. Applicants submit that the artisan knows that there is no definite correlation between the presence of antibodies and protective immunity as demonstrated in the specification at pp. 15-16 of the specification and that if the levels are not predictive then there is no expectation of enhanced protective effect with adjuvant. Applicants acknowledge that Estrada causes increased absorption through mucosal membranes but argue that the reference does not teach or suggest that saponin stimulates protective mucosal immunity in challenge and thus that there is no reasonable prediction of protection provided by immunization with Quinoa saponins.

In response, it is unclear how Estrada's teachings are still considered unexpected with respect to Quil A as Estrada notes IgG and IgA production via Quillaja and Quinoa saponins. While Estrada notes that IgA responses had not yet been noted for Quillaja, Estrada clearly shows that as of at least 1-28-1997 IgA and IgG stimulation are known for Quillaja and Quinoa saponins and would not be unexpected as of the filing date of instant '385, 1-15-1998. Applicant's arguments with respect to the predictability of the immune response upon challenge is jointly addressed in Timoney, Hartford and Estrada. For example, instantly claimed vaccine (live non-encapsulated attenuated S. equi) is the same as Timoney with the sole exception of saponin adjuvant.

Timoney has already established in the art that the claimed live non-encapsulated attenuated S. equi vaccine stimulates the appropriate immune responses such that protective immunity is established in the host in response to challenge, including IgG and IgA even without adjuvant, see in particular Figures 1-3, Columns 5-6 and Claims 1-10. Thus, the specificity of the vaccine is established. It is known in the art as exemplified by Hartford and Estrada that Quillaja and Quinoa saponins are adjuvants which enhance antigen specific immune responses in the host when co-administered with the appropriate antigens, and that saponins predictably and specifically stimulate mucosal immunity through enhanced mucosal absorption and production of antigen specific IgG and IgA, see in particular Hartford, p. 3 and Estrada, columns 5-6, as noted above. Thus, the predictive effects do not appear to be of question. It is also noted that sero conversion per. se., is not required but merely IgG and/or IgA mucosal production. The artisan would expect only improved vaccination effects by inclusion of a saponin adjuvant with the Timoney vaccine, the specificity of the vaccine already having been established by Timoney.

In paragraph 9 of the traversal on 3-13-02 Applicants argue that Estrada does not teach the use of S. equi or other bacterial or disease causing antigens but that Estrada uses avidin and cholera toxin which are known adjuvants as exemplified by Hartford, p. 3, lines 39-44. Applicants conclude that thus Estrada teaches non-specific immunological responses to adjuvants by administration of saponin and that the artisan could not predict protection against contact with a specific disease based on Estrada's teachings.

In response, it is not Estrada's teachings that are solely relied upon, but the cumulative teachings of Timoney, Hartford and Estrada as set forth above.

In paragraphs 10-11 of the traversal on 3-13-02 Applicants argue that the artisan could not predict a protective immune response using any saponin type, in particular as Estrada teaches the benefits of Quinoa saponin which are unexpectedly different from Quillaja saponin. Applicants again argue that Estrada fails to use disease specific antigen and that Quinoa saponins rather than Quillaja saponins enhance nonspecific immunity and cause increased absorption through mucosal membranes. Evidence of unexpectedness is noted at col. 2, lines 25-27 and that thus the artisan could not expect the properties of any type of saponin used as an adjuvant. Based on the aforementioned teachings Applicants conclude that Estrada does not supply the suggestion or motivation missing from Hartford and Timoney to render the invention obvious.

In response, as noted above Estrada is not unexpected as of the patent publication date. The benefits of Quillaja and Quinoa saponins in the stimulation of enhanced mucosal immunity as exemplified by enhanced mucosal absorption, IgG and IgA production are noted in Estrada. The specificity of the Timoney vaccine is established. Hartford also suggests the inclusion of adjuvants for enhancing the immune response in S. equi vaccination of animals, and specifically for mucosal immunity. Thus, Estrada and Hartford both provide suggestion and motivation to modify the Timoney vaccine by inclusion of saponin adjuvants.

In paragraphs 12-15of the response of 3-13-02, Applicants note the Examiner's previous assertion that Timoney at col. 6, lines 30-31 teach that "the mouse has historically been the model for the immunology of S. equi infection." However, Applicants conclude that all this teaches is the study of the immune response in mice to potential equine vaccines. Applicants argue that Timoney did not extrapolate the data in mice to conclude or suggest a similar effect in horses. Applicants argue that Hartford

did not establish protective effects in horses, but only in mice using the mouse model. Applicants again suggest that Hartford did not extrapolate or suggest similar effect in horses. Applicants further argue that even though Hartford did test the vaccine in horses, the test was only for safety and not efficacy, and that the artisan could not conclude efficacy without actually performing the tests in horses. Applicants argue that the Examiner's conclusion of intrinsic immunity is not supported by the reference teachings and is constructed by hindsight reasoning and that the artisan could, at best only be motivated to combine Hartford, Estrada and Timoney based on the present invention because Timoney is silent to adjuvants which would provide the enhanced protective immunological effect demonstrated by the claimed saponin and the attenuated S. equi vaccine.

In response, it is noted that Timoney not only suggests that the mouse model is capable of extrapolation to horses, Timoney shows that it is extrapolatable by showing that the protective effects in horses are indeed exemplified in mice. In particular, Timoney directly compares in a "parallel test of efficacy" horses and mice, see in particular column 5, line 7-column 6, line 5 and column 6, line 29-line 54. Hartford also includes experimentation in mice, and horses. Hartford's safety, treatment, vaccination/challenge and protection studies are directed to both mice and horse vaccines, but are especially contemplated for use in treatment of horses, see in particular p. 2, lines 1-49 and p. 3, lines 6-10, "the invention further provides a live vaccine for combating Streptococcus infection in horses." In addition, to the experimentation in mice, (see in particular Examples III-IV), Example V, teaches that the protective results noted in mice are comparable those noted in horses. In particular, six horses were inoculated and followed to 4 weeks post/challenge. No mortality nor clinical signs of infection were noted, in particular there were no sudden temperatures

nor abscesses formed in the mandibular and pharyngeal lymph nodes, see in particular p. 12, Clinical signs and Post-mortem examination. Thus, the prevailing evidence of the references establishes, even in the safety studies of Hartford, that prior to Applicant's invention, the S. equi vaccines or the prior art were known to be similarly protective and predictive in both horse and mouse models as disclosed.

Finally, in paragraph 16-20, of 3-13-02 Applicants point to the declaration of 6-29-01 and conclude therefrom that the invention is thus not obvious in light of Timoney, Hartford and Estrada, alone or in combination. In particular, that the prior art fails to render obvious that the S. equi vaccine when combined with saponin, would exhibit enhanced immunostimulatory and protective effects as a result of the addition of saponin.

Applicant's declaration filed 6-29-01 has been fully considered but is not persuasive. In particular, the Examiner notes that the comparison delineated in the declaration is between the instantly claimed vaccination and a commercial vaccine of Carbopol/S. equi enzyme extract administered intra-muscularly. Such evidence is insufficient to show an unexpected difference in the vaccine of Timoney and the vaccine of Timoney when modified by the inclusion of saponin, particularly as the Timoney, Hartford and Estrada reference teachings cumulatively suggest that the saponins' inclusion would specifically enhance the protective immune response stimulated by the Timoney vaccine alone. Additionally, it is noted that there is no evidence of record which would contradict the efficacy of any adjuvant or of saponin in particular from exhibiting such effects, in particular as noted for the benefits of mucosal administration and immunity.

Although not relied on for the rejection, it is again noted that the skilled artisan recognizes as set forth in Timoney et al., Recent advances in streptococci and

streptococcal diseases (1985) pp. 294-5, Proceed. Of the IXth Lancefield Int'l Symp. on Strep. and Strep. Diseases, Japan, September 1984, Reedbooks Ltd., Chertsey, that cumulative findings suggest that successful vaccination requires stimulation of the nasopharyngeal immune response and that vaccination with 709-27 stimulates IgA and IgG antibodies even in the absence of Q. Saponin adjuvant, see in particular Figure 1.

The references cumulatively provide both the suggestion of making the invention and an expectation of success. Therefore the claimed invention is rendered obvious to the skilled artisan at the time of the invention.

It is further noted that the amended language "for providing protective immunity against Streptococcus equi infection following Streptococcus equi challenge" is non-limiting to the composition and similarly contributes no further steps in any methods as recited. The limitation is akin to a recitation of intended use without the addition of further limiting active steps. However, to the extent to which the recitation implies that the method be administered "following Streptococcus equi challenge", it is unclear that applicants have support for such language as no support was provided by page and line number at the time of entry. For search and examination purposes the recitation has received no weight. The recitation "for providing protective immunity against Streptococcus equi infection" is non-limiting but has been specifically addressed in the rejection above as the vaccine of Timoney has already been found to provide protective immunity against Streptococcus equi infection regardless of the addition of adjuvant. The above discussions exhibit that the artisan would expect increase the protective immunity/antibody response/prevention of symptoms already provided by the Timoney vaccine.

Applicants additionally argue in the response of 11-12-02 that the Examiner's rejection fails to establish that the combined materials are effective in horses, since the

only objective suggestion for such a combination in horses in found in the instant application. In addition Applicants present arguments as to indicia of unobviousness in unexpected superiority (of the vaccine) leading to commercial success and satisfaction of a long felt need. In particular Applicants submit a declaration under 37 CFR 1.132 of Robert Daily to establish commercial interest, success and long felt need of the claimed invention that is argued to result from the superiority of the claimed invention.

In response, the PTO has insufficient facilities for testing or comparing multiple vaccine preparations. While the Examiner's rejection fails to definitively establish that the combined materials are effective in horses, this does not appear to be a grounds for removal of the rejection of record. The Examiner has not questioned the findings of Applicants specification that the combined materials are effective in horses. Instead, the Examiner has presented a case whereby such findings are obvious in light of the cumulative prior art teachings. The comparison of the prior art vaccine with or without adjuvant has yet to be performmed by Applicants and presented to the Office for consideration. As to the objective suggestion for the combination of materials in horses, the Examiner relies on the cumulative reference teachings of Timoney, Hartford and Estrada as extensively discussed in the record. In reiteration of above, it is noted that Timoney not only suggests that the mouse model is capable of extrapolation to horses, Timoney shows that it is extrapolatable by showing that the protective effects in horses are indeed exemplified in mice. In particular, Timoney directly compares in a "parallel test of efficacy" horses and mice, see in particular column 5, line 7-column 6, line 5 and column 6, line 29-line 54. Hartford also includes experimentation in mice, and horses. Hartford's safety, treatment, vaccination/challenge and protection studies are directed to both mice and horse vaccines, but are especially contemplated for use in treatment of horses, see in particular p. 2, lines 1-49 and p. 3, lines 6-10, "the invention further

provides a live vaccine for combating Streptococcus infection in horses." In addition, to the experimentation in mice, (see in particular Examples III-IV), Example V, teaches that the protective results noted in mice are comparable to those noted in horses. In particular, six horses were inoculated and followed to 4 weeks post/challenge. No mortality nor clinical signs of infection were noted, in particular there were no sudden temperatures nor abscesses formed in the mandibular and pharyngeal lymph nodes, see in particular p. 12, Clinical signs and Post-mortem examination. Thus, the prevailing evidence of the references establishes, even in the safety studies of Hartford, that prior to Applicant's invention, the S. equi vaccine of the prior art were known to be similarly effective to evoke an immune response, protective against mortality (a symptom) and predictive in both horse and mouse models as disclosed.

Applicant's 37 CFR 1.132 declaration via Robert Daily has also been fully considered but is not persuasive. As to the declaration Point 4 speaks to the commensurate scope of the product Pinnacle TM with the claimed composition and route of administration. Point 5 speaks to increases in units sold and gross sales since the products introduction into the market along with a decrease in sales of a competitive killed S. Equi product and state that the decrease in sales of the killed vaccine resulted from entry of Pinnacle TM to the commercial market. Point 6 concludes that the sales data establish commercial succes and significant impact in the market. The declaration statest that Pinnacle provides a safe and effective alternative to traditionally reactive intramuscular vaccines and that the increased sales reflect product superiority. The declaration states that the commercial success results from the attenuated bacterium combined with saponin.

In response to points 5 and 6, the comparison presented is between sales data for Pinnacle $^{TM}$ (which is representative of the claims although the dosage is not noted)

and a Bayer killed S.equi product. The data notes that since Pinnacle's introduction to the market, units sold and gross sales have increased while in the third quarter of 1999 sales of the Bayer product declined from the prior year coinciding with entry of Pinnacle to the commercial market. While this data tends to support increased market share, the evidence of record is insufficient to conclude such as there is no disclosure of the corresponding variables for the remainder or even to a large proportion of the total market. For example sales may increase due to the price per unit being cheaper than the competitor or due to aggressive marketing tactics. Yet more importantly the comparison presented is not one of the claims in comparison to the closest prior art as set forth in the rejection, i.e., Timoney that is the claimed vaccine but without the combination of saponin. The MPEP notes that commercial success must flow from the functions and advantages disclosed or inherent in the description in the specification and may not be attributable to improvements or modifications made by others, see in particular MPEP 716.03(b) and In re Vamco Machine & Tool, Inc., 752F.2d 1564, 224 USPQ 617 (Fed. Cir. 1985). There is no evidence as to what market share or commercial success the Timoney vaccine enjoys. Moreover, the Timoney vaccine is already recognized as a solution to S. equi infection. The invention by Applicants is a supposed improvement of Timoney by the addition of saponin. Yet even here the improvement is deemed to be the invention of another because Hartford and Estrada have already taught the addition of saponin to S. equi vaccines so as to enhance the immune response. The modification claimed is a solution already recognized in the art. As no comparison of the instant vaccine with the vaccine of Timoney has been performed, no conclusion of non-obviousness can be concluded. All the specification appears to add is evidence that the expected properties are provided. Moreover, Applicants arguments as to long felt need do not appear to arise to evidence of non-

obviousness because S. equi vaccines are known as for example in the Timoney vaccine, are in practice and are known to be successful. Thus, Applicants arguments and the declaration are insufficient to overcome the obviousness rejection of record.

**Status of Claims**

8. No claims are allowed.

**Conclusion**

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
February 26, 2003

Gary L. Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600